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# Chloride Ion Catalyzed Conformational Inversion of Carbocation Intermediates in the Hydrolysis of a Benzo[*a*]pyrene 7,8-Diol 9,10-Epoxide

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***Abstract:*** A highly efficient procedure for converting 7*β*,8α-dihydroxy-9α,10α-epoxy-7,8,9,10-tetrahydrobenzo[*a*]pyrene (**1**) to its *trans*-9,10-chlorohydrin (**5**) with excellent yield and purity by the reaction of anhydrous HCl in THF has been developed. The rate of reaction of **5** has been determined as a function of sodium chloride concentration in 1:1 dioxane−water solutions. A large common ion rate depression for the reaction of the chlorohydrin was observed, and the rate data are fit to a mechanism in which all of the tetrol products are formed by the reaction of water with the C-10 carbocation intermediate. Yet, the cis/trans ratio of tetrols from the reaction of the carbocation intermediate from the hydrolysis of chlorohydrin **5** is different than the cis/trans tetrol ratio from the acid-catalyzed hydrolysis of diol epoxide **1**, which hydrolyzes via a carbocation with the same connectivity as that formed in the hydrolysis of **5**. To rationalize these results, it is proposed that the $S_N1$ reaction of chlorohydrin **5** yields a different distribution of carbocation conformations than that formed from the reaction of **1** with $H^+$. The energy barrier for the inversion of these carbocation conformations must be large relative to the energy barriers for the reaction of each carbocation conformation with water. In solutions containing sufficient concentrations of chloride ion, however, a lower energy pathway via a halohydrin exists for the interconversion of the carbocation conformations. Thus, chloride ion catalyzes the interconversion of these two carbocation conformations.

## Introduction

The rates[1] and products of the hydrolysis reactions[1−4] of the 7,8-dihydroxy-9-10-epoxide metabolite (**1**) of the environmental carcinogen benzo[*a*]pyrene have been thoroughly studied. At pH < ∼7 in 10:90 dioxane−water, **1** reacts with $H^+$ to form a triol carbocation **2**, which reacts with water to form trans 9,10- and cis 9,10-tetrols **3** and **4** in a 94:6 ratio. In this reaction, epoxide ring opening is rate-limiting, and carbocation **2** has a sufficient lifetime in water solutions to react with external nucleophiles such as azide[5] and halide[6,7] ions.

The reaction of **1** in solutions containing chloride ion, however, yields significantly more cis tetrol (∼35%) than that formed from the reaction of **1** in the absence of chloride ion.[6] To explain the different tetrol product ratios formed from the reaction of diol epoxide **1** in solutions containing chloride ion, it was proposed that a trans chlorohydrin **5** is formed as a reactive intermediate from the reaction of carbocation **2** with chloride ion, and that **5** hydrolyzes to form cis and trans tetrols in a ratio different than that formed from the reaction of **1** in the absence of chloride ion (Scheme 1). This proposed mechanism was confirmed by the independent synthesis of chlorohydrin **5** and a study of its hydrolysis reactions.[8,9] Chlorohydrin **5** is highly reactive toward hydrolysis and yields tetrols in the same ratio as that formed from the reaction of diol epoxide **1** in solutions containing sufficient concentrations of chloride ion.

It has also been observed that the covalent adducts from reaction of **5** with deoxyadenosine and with DNA have mostly cis 9,10-stereochemistry,[8] whereas the covalent adducts from the reaction of diol epoxide **1** with DNA in the absence of chloride ion have mostly trans 9,10-stereochemistry.[6,10,11] There are significant cellular concentrations of chloride ion (∼10 mM), and therefore, chlorohydrin **5** may be formed from the reaction of diol epoxide **1** in vivo; thus, **5** may play a role in chemical

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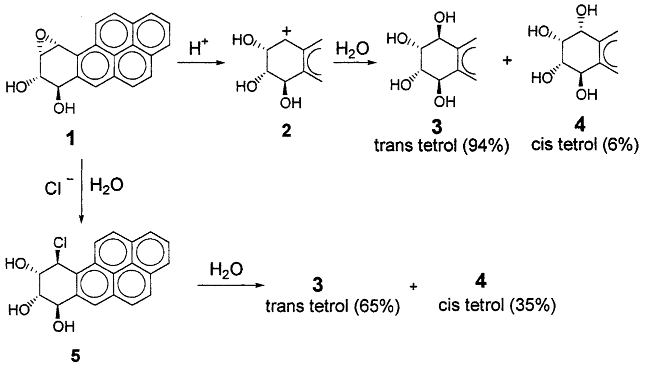
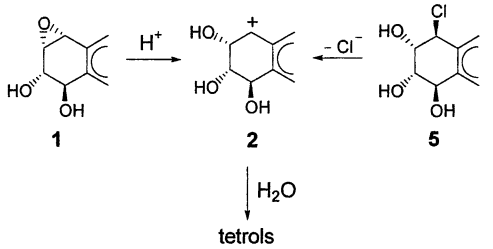
Scheme 1



Scheme 2



carcinogenesis.[6] At $[Cl^-] = 10$ mM, it can be calculated that ~10% of carbocation **2** is trapped by chloride ion in water solution to form **5**.[7]

The observation that trans chlorohydrin **5** undergoes hydrolysis to yield more cis tetrol than the acid-catalyzed hydrolysis of diol epoxide **1** in the absence of chloride ion is particularly intriguing. The reaction of **1** with $H^+$ and the $S_N1$ reaction of chlorohydrin **5** are expected to yield the same carbocation intermediate (Scheme 2). If tetrol products are formed from this intermediate with water, then the acid-catalyzed hydrolysis of diol epoxide **1** and the hydrolysis of chlorohydrin **5** by the $S_N1$ mechanism would yield the same tetrol mixture, contrary to the actual observation. The hydrolysis of **5** in solutions containing chloride ion is reported to be slower than in solutions without chloride ion,[8] which suggests that **5** reacts at least in part via a carbocation intermediate. To explain the greater yields of cis tetrol and of cis nucleic acid adducts from reactions of diol epoxide **1** in the presence of chloride ion, it was proposed that the intermediate trans chlorohydrin **5** undergoes $S_N2$ reactions with water to yield cis tetrol and with nucleic acids to yield cis adducts.[6,9,12]

From plots of the cis:trans tetrol ratio from the reaction of **1** versus the concentration of chloride ion, it can be concluded that part or all of the tetrols from hydrolysis of chlorohydrin **5** must be formed by a mechanism distinct from that for the hydrolysis of **1**.[7] Another pathway for the reaction of **5** to form tetrol(s) must exist. In addition to the $S_N2$ reaction of **5** with water proposed as one possible pathway,[6,9,12] other possible mechanisms for the hydrolysis of **5** include a rate-limiting reaction of a carbocation−chloride ion pair with solvent and the ionization of **5** to give a discrete carbocation having a conformation different from that formed when **1** reacts with $H^+$.[7] In this paper, we summarize rate data for the reactions of trans chlorohydrin **5** in dioxane−water solutions containing chloride ion and conclude that **5**, like diol epoxide **1**, hydrolyzes exclusively via a discrete carbocation intermediate. A rationale for the observation that the acid-catalyzed hydrolysis of diol epoxide **1** and the hydrolysis of chlorohydrin **5** yield different hydrolysis product mixtures is provided.

## Experimental Section

**Materials and Methods.** (±)-7β,8α-Dihydroxy-9α,10α-epoxy-7,8,9,10-tetrahydrobenzo[*a*]pyrene (**1**), in which the benzylic 7-hydroxyl group and epoxide oxygen are trans, was prepared by published procedures.[4,13] This material is carcinogenic and should be handled with caution. Dioxane and THF were distilled from sodium prior to use. All other reagents were purchased from commercial sources. NMR spectra were recorded at 200 MHz. HPLC analyses of tetrols **3** and **4** were carried out as previously described.[7] Quantum-chemical calculations were performed with the molecular modeling program Titan, from Wavefunction, Inc.-Schrödinger, Inc.

**Synthesis of Chlorohydrin 5.** A solution of 0.40 mL of 4 M HCl in dioxane and 0.2 mL of anhydrous THF was added to a solution of 5.4 mg of diol epoxide **1** in 0.80 mL of anhydrous THF. The resulting solution was swirled and allowed to stand at room temperature for 2 min. The solvent and excess HCl were removed by rotary evaporation at reduced pressure to yield 7.0 mg of residue. The $^1H$ NMR spectrum of the product, supplied as Supporting Information, indicated that there was a clean conversion of **1** to chlorohydrin **5**: $^1H$ NMR (THF-$d_8$) $\delta$ 6.11 (d, $J = 2.8$ Hz, H−C(10)), 5.09 (d, $J = 9.1$ Hz, H−C(7)), 4.55 (m, H−C(9)), 4.29 (dd, $J = 9.1$, 2.1 Hz, H−C(8)). These NMR data are very similar to those reported[8] for **5** in DMSO-$d_6$ and support the trans 9,10-stereochemistry. The H−C(7)−C(8)−H coupling constant of 9.1 Hz is very similar in magnitude to the 7,8-coupling constant of the corresponding 7,8,9,10-tetrahydro-7,8,9,10-tetraacetate with a trans 9,10-stereochemistry.[4] All coupling constants for the C(7)−C(10) hydrogens of the 7,8,9,10-tetrahydro-7,8,9,10-tetraacetate with a cis 9,10-stereochemistry are small (2−3 Hz).[4] The H−C(7)−C(8)−H coupling constant of 9.1 Hz and the H−C(9)−C(10)−H coupling constant of 2.1 Hz suggest that the principal conformation of **5** is **5a** (cf Scheme 5), in which the hydrogens on C(7) and C(8) are in a trans, pseudo-diaxial geometry and the hydrogens on C(9) and C(10) are pseudo-diequatorial.[4,8] This product was used without further purification for kinetic and product studies. The rate of reaction of **5** in 1:1 dioxane−water is independent of pH at pH < 9. At pH > 10, the rate of reaction of **5** increases with the increase of pH. The fitting of these rate data to the equation $k_{obsd} = k_o + k_{OH}[HO^-]$ yielded values of $k_o = (2.7 \pm 0.1) \times 10^{-2}\ s^{-1}$ and $k_{OH} = (1.40 \pm 0.05) \times 10^{2}\ M^{-1}\ s^{-1}$. The magnitude of the second-order rate constant for the reaction of **5** with hydroxide ion at pH > 10 is consistent with that expected for the reaction of a trans chlorohydrin with hydroxide ion to form an epoxide,[14] in this case diol epoxide **1**.[8] A plot of $k_{obsd}$ versus pH for the reaction of **5** in 1:1 dioxane−water is provided as Supporting Information.

**Kinetic Procedures.** For each kinetic run, approximately 5 μL of a stock solution of **5** in dioxane (1 mg/mL) was added to 2.0 mL of 1:1 dioxane−water solution in the thermostated cell compartment (25.0 ± 0.2 °C) of a UV−vis spectrophotometer. Reactions were monitored at 344 nm, and pseudo-first-order rate constants were calculated by nonlinear regression analysis of the absorbance versus time data.

**Product Studies.** The products from the reaction of **5** in 10:90 dioxane−water solutions were determined by reverse phase HPLC analyses of the reaction solutions after >10 half-lives on a $C_{18}$ column with 60:40 methanol−water as eluting solvent.[7] Products were monitored by UV detection at 269 nm. The relative yields of cis and trans tetrols from the reaction of **5** in 10:90 dioxane−water solution containing $NaClO_4$ (0−0.5 M) at pH 4 remained constant at 78−79% trans and 21−22% cis. The relative yield of cis tetrol from the reaction

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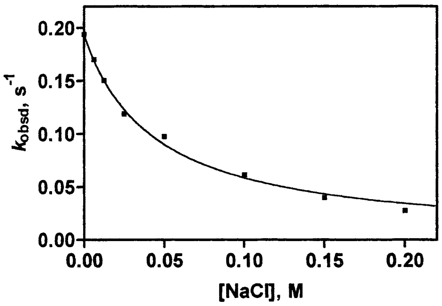
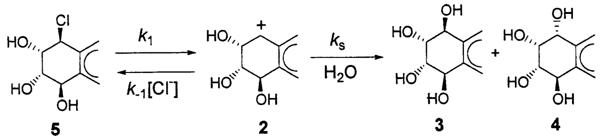


***Figure 1.*** Plot of $k_{obsd}$ vs [NaCl] for the reaction of **5** in 1:1 dioxane−water solution, $\mu = 0.2$ M ($NaClO_4$).

***Scheme 3***



of **5** in 10:90 dioxane−water increased from ~21% when NaCl was absent to 35% in 1.0 M NaCl solution.

The relative yields of cis tetrol from the acid-catalyzed hydrolysis of diol epoxide **1** in water,[1] 10:90 dioxane−water,[1,7] and 25:75 dioxane−water[1] are reported to be 14−19%, 6−8%, and 4−5%, respectively. The relative yield of cis tetrol from the acid-catalyzed hydrolysis of **1** in 10:90 dioxane−water increases from 6% in the absence of NaCl to 35% in 1.0 M NaCl solution.[7]

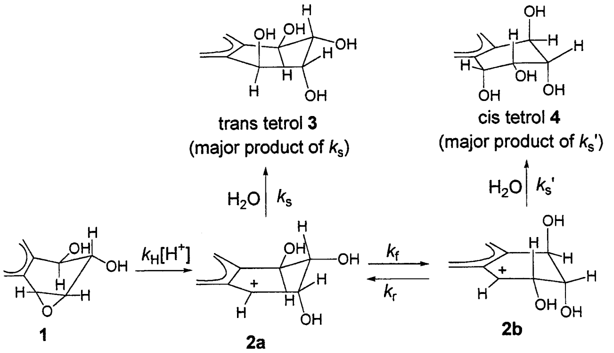
## Results

Trans chlorohydrin **5** has been synthesized by the reaction of diol epoxide **1** with lithium chloride and acetic acid in THF.[8] In our hands, this procedure yielded a mixture of products that were not readily separated and purified. In an alternate approach, we have synthesized **5** in high yield by the reaction of **1** with anhydrous HCl in THF. The product from this reaction was sufficiently pure for kinetic and product studies without further purification.

The rate of reaction of **5** in 1:1 dioxane−water was determined as a function of increasing concentration of sodium chloride at constant ionic strength maintained by the addition of sodium perchlorate, and a plot of these data is provided in Figure 1. These data show a marked common ion rate depression for the reaction of **5**, which is consistent with the mechanism outlined in Scheme 3. In this mechanism carbocation formation ($k_1$) is rate-limiting in the absence of chloride ion, and capture of the carbocation by solvent ($k_s$) is rate-limiting at high chloride ion concentrations. This “common ion effect” demonstrates that there is an intermediate in the reaction that is captured by chloride ion and converted back to a reactant, thus slowing the reaction. The rate of reaction of **5** in 0.2 M sodium chloride solution is 7.5 times slower than that of its reaction in the absence of chloride ion. With the assumption that carbocation **2** is a steady-state intermediate in the hydrolysis of **5**, the rate expression for the mechanism of Scheme 3 is given by eq 1. The rate data in Figure 1 fit eq 1 and yielded values of 0.19 ± 0.01 s$^{-1}$ and 23 ± 2 M$^{-1}$ for $k_1$ and $k_{-1}/k_s$, respectively. The kinetic data thus fit a mechanism in which all of the tetrol product is derived from the capture of a discrete carbocation intermediate by water and rule out both a mechanism in which the cis tetrol (35%) is formed from an $S_N2$ reaction of trans chlorohydrin **5** with water and a mechanism involving the reaction of an ion pair with water. The latter reaction pathways would have rates that are not depressed by added chloride ion, and if these latter pathways were significant, then the rate profile for the reaction of **5** in solutions containing chloride ion (Figure 1) would be asymptotic to a nonzero rate constant. In summary, the tetrol-forming steps from both the acid-catalyzed hydrolysis of diol epoxide **1** and the hydrolysis of chlorohydrin **5** must involve only the attack of water on discrete carbocation intermediates. Mechanisms for tetrol formation involving the reactions of “intimate” or “solvent-separated” ion pairs with water are ruled out, since increasing chloride ion concentration would not reverse the formation of such ion pairs.

$$k_{obsd} = \frac{k_1}{(1 + k_{-1}[Cl^-]/k_s)} \tag{1}$$

***Scheme 4***



## Discussion

A number of intriguing observations in the hydrolysis reactions of **1** and **5** need to be rationalized: (1) the acid-catalyzed hydrolysis of diol epoxide **1** and the hydrolysis of chlorohydrin **5** yield tetrols with different cis/trans ratios, even though each reaction proceeds via a discrete carbocation intermediate and both reactions might be expected to yield identical cis/trans product ratios; (2) the reactions of both diol epoxide **1** and chlorohydrin **5** in solutions of high chloride ion concentrations yield the same cis/trans ratio of tetrols; and (3) the cis/trans tetrol ratio from the hydrolysis of chlorohydrin **5** in solutions with high chloride ion concentrations is somewhat different than that from the hydrolysis of **5** in the absence of chloride ion (Experimental Section).

**Reaction of Diol Epoxide 1.** The acid-catalyzed hydrolysis of **1** occurs by rate-limiting epoxide ring opening to form a carbocation **2**, which has a sufficient lifetime to react with external nucleophiles at rates greater than that with which it reacts with water.[5] The reaction of **1** with H$^+$ from its more stable ground-state conformation yields carbocation **2a**, which can undergo ring inversion to yield a second carbocation conformation, **2b** (Scheme 4). Carbocation conformations **2a** and **2b** are substituted cyclohexenyl carbocations, and it has been shown that the axial attack of water on cyclohexenyl carbocations is favored over equatorial attack.[15,16] A benzylic carbocation that is constrained to a geometry related to **2a**, which contains an axial hydroxyl group adjacent to the carbocationic

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carbon, yields >99% of trans diol by an axial attack of water.[17] An isomeric benzylic carbocation that is constrained to a geometry related to that of **2b**, which contains an equatorial hydroxyl group adjacent to the carbocationic center, yields ~75% of cis diol from an axial attack of water and ~25% of trans diol from an equatorial attack of water.[17] By analogy, an axial attack of water on **2a** to yield trans tetrol **3** should be strongly favored. An axial attack of water on **2b** to yield cis tetrol **4** should also be favored, but to a lesser extent. An equatorial attack of water on **2b** to yield trans tetrol **3** might also be expected to occur as a minor reaction pathway. The observation that the acid-catalyzed hydrolysis of **1** yields mostly trans tetrol (~94%) can, therefore, be explained by either of the following two mechanisms in which most of the tetrol product is derived from an axial attack of water on **2a**: (1) **2a** and **2b** are in rapid equilibrium, and an attack of water on **2a** is energetically favored over attack of water on **2b** or (2) epoxide ring opening favors the formation of **2a**, and the rate of attack of water on **2a** ($k_s$) is greater than the rate of conformational inversion of **2a** to **2b** ($k_f$). We had previously[17] favored the first interpretation, since we had assumed that the conformation **2a** was preferred at equilibrium because it has one less gauche butane interaction than **2b**. An axial attack by water on the predominant **2a** rather than on the higher-energy **2b** could then provide a more favorable pathway to products, resulting in trans tetrol. However, our present results (see below) are inconsistent with mechanism (1) and support the alternative mechanism (2); namely that **2a** and **2b** are of comparable stabilities, but initially formed **2a** is not in rapid equilibrium with **2b** relative to solvent attack.

**Reaction of Chlorohydrin 5.** The common ion rate depression for the hydrolysis of chlorohydrin **5** (Experimental Section) fits a rate equation that is asymptotic to zero at high chloride ion concentration and, thus, requires that all of the tetrol product must be formed from the reaction of water with an intermediate (i.e., a carbocation) whose stoichiometry does not include chloride ion and, thus, cannot involve any type of ion pair. If the reactions of both **1** and **5** form the same carbocation and tetrol products are formed from this carbocation, then the tetrol products formed from the hydrolyses of **1** and **5** should be identical. Yet, the ratio of cis 9,10- and trans 9,10-tetrols from reactions of **1** and **5** are different. Thus, there must be two distinct populations of the carbocation intermediate that interconvert more slowly than they react with solvent. These two populations could consist of different solvation states or different conformations. We first considered that the hydrolysis of chlorohydrin **5** and the acid-catalyzed hydrolysis of diol epoxide **1** give carbocations in different solvation states that could possibly yield tetrols with different cis:trans ratios. The rate of reaction of carbocation **2** with water has been estimated to be $\sim 2 \times 10^7$ s$^{-1}$,[5] whereas solvent relaxation occurs within $10^{-13}$–$10^{-11}$ s,[18] which is many orders of magnitude faster than the rate at which **2** reacts with solvent. Thus, we conclude that different solvation states of a carbocation would equilibrate too rapidly to account for the observed product differences. We are, therefore, left to conclude that the ionization of **5** yields a different distribution of carbocation conformations than that formed from the reaction of **1** with H$^+$ and that the energy barrier for the interconversion of these conformations must be greater than the energy barrier for the reaction of each carbocation conformation with water.[19]

From the partitioning of carbocation **2** between the reaction with water and the addition of azide ion, with the assumption that azide ion reacts with **2** at the diffusion-limited rate constant of $5 \times 10^9$ s$^{-1}$, a value of $k_s$ for the reaction of **2** with water is estimated to be $\sim 2 \times 10^7$ s$^{-1}$.[5] From this rate constant, the energy barrier for the reaction of **2** with water is calculated to be 7.5 kcal/mol. In a preliminary calculational study, gas-phase structures of carbocation conformations **2a** and **b** and a transition structure for their interconversion have been calculated at the ab initio B3LYP/6-31G* level of theory.[20] Conformation **2a** is calculated to be 0.03 kcal/mol more stable than conformation **2b**, and the energy difference between the transition structure and conformation **2a** is calculated to be 7.92 kcal/mol.[20] Although differences in solvation effects, zero point energy, and temperature were not taken into account, the calculated structures are consistent with our proposal that carbocation conformations **2a** and **b** have similar energies and that the barrier to their interconversion is greater than the energy barriers for their reactions with solvent.

**Mechanistic Considerations.** At chloride ion concentrations > ~0.1 M, the rate of reaction of chloride ion with carbocation **2** exceeds the rate of reaction of water with **2**.[7] The reactions of diol epoxide **1**with HCl/THF or LiCl/HOAc yield only trans chlorohydrin **5**, and this chlorohydrin is most likely the major product from the reaction of **2** with chloride ion in water solution and may be the intermediate responsible for the different cis/trans tetrol ratio from the hydrolysis of **1** when chloride ion is present in solution. However, the intermediacy of a cis chlorohydrin in the hydrolysis of **1** cannot be ruled out. Regardless of the cis/trans composition of chlorohydrin intermediates in the hydrolysis of diol epoxide **1** in the presence of chloride ion, the relative amounts of carbocation conformations **2a** and **b** from chlorohydrin hydrolysis must be different than that formed from the acid-catalyzed epoxide ring opening of diol epoxide **1**.

One possible mechanism for the acid-catalyzed hydrolysis of diol epoxide **1** in the presence of chloride ion involving only trans chlorohydrin **5** as an intermediate is provided in Scheme 5. If cis chlorohydrin is also an intermediate, then the mechanism will be more complicated. In the mechanism of Scheme 5, the energy barrier for interconversion of carbocation conformations **2a** and **b** is greater than the energy barriers for the reaction of each carbocation conformation with water. Diol epoxide **1** reacts with H$^+$ primarily from its more stable ground-state conformation to form carbocation **2a**. When chloride ion is not present in solution, conformation **2a** reacts with water to yield trans tetrol faster than it undergoes conformational isomerization to **2b**. However, it has been established that, if chloride ion is present in sufficient concentration, then the carbocation intermediate (i.e., conformation **2a**) reacts with chloride ion to yield trans chlorohydrin **5** faster than it reacts with solvent.[7]

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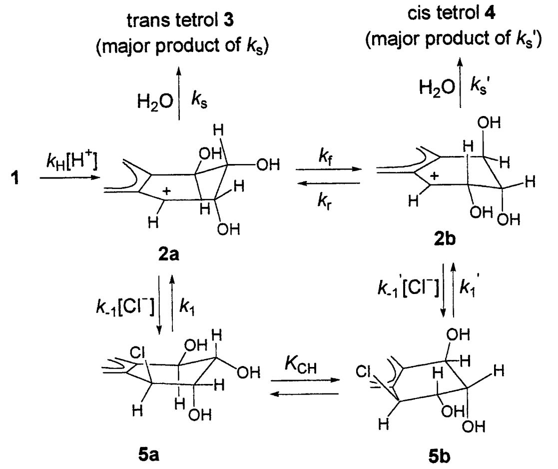
[19] In the acid-catalyzed methanolysis of K-region arene oxides, a mechanism in which the rate of solvent capture of a carbocation intermediate is comparable to that of its conformational inversion is proposed: Nashed, N. T.; Bax, A.; Loncharich, R. J.; Sayer, J. M., Jerina, D. M. *J. Am. Chem. Soc.* **1993**, *115*, 1711−1722.

[20] Calculated structures, energies,Cartesian coordinates of **2a** and **b** and a transition structure for their interconversion are provided as Supporting Information.

*Scheme 5*



Quantum chemical calculations indicate that there are two principal conformations of chlorohydrin **5**, one in which hydroxyl groups occupy equatorial positions and the C−Cl bond is oriented 74° out of the plane of the aromatic system (**5a**) and a second in which the two hydroxyl groups occupy axial positions and the C−Cl bond is oriented 59° out of the plane of the aromatic system (**5b**).[21] Therefore, ionization of **5a** to form carbocation **2a** and ionization of **5b** to form carbocation **2b** can each occur without large changes in molecular geometry. The capture of carbocation **2a** by chloride ion, conformational inversion of **5a** to **b**, and ionization of **5b** to form carbocation **2b**, therefore, provide one of several possible indirect routes for carbocation inversion.

NMR coupling constants indicate that **5** exists primarily as conformation **5a** (see Experimental Section), and this conclusion is supported by quantum chemical calculations. Conformation **5a** is calculated at the HF/6-31G* level of theory to be 4.66 kcal/mol more stable than conformation **5b**, and a transition structure for their interconversion has been calculated to be 11.52 kcal/mol less stable than that of **5a**. This calculated energy barrier for the conversion of **5a** to **b** is much less than the free energy for the hydrolysis of **5** (calculated to be 18.4 kcal/mol from rate data), and therefore, these two conformations should be at equilibrium during the hydrolysis of **5**. The relative rates of formation of carbocation conformations **2a** and **b** from chlorohydrin **5** do not depend on the energy difference between **5a** and **b**, however, but rather on the energy difference between the transition states for the formation of **2a** and **b** from the reaction of **5** (Curtin−Hammett principle).[22]

The observation that chlorohydrin **5** yields cis and trans tetrols in a ratio different than that formed from the acid-catalyzed hydrolysis of diol epoxide **1** requires that the rate of interconversion of **2a** and **b** must be slow relative to the rates of their reactions with water ($k_s$ and $k_s'$, respectively). Therefore, during the hydrolysis of **1** in the absence of chloride ion, the two carbocation conformations, **2a** and **b**, are not at equilibrium. They will be at equilibrium during the hydrolyses of diol epoxide **1** and chlorohydrin **5** in solutions containing high concentrations of chloride ion, however. Under this condition, **2a** and **b** must be in equilibrium because of the thermodynamic cycle outlined in Scheme 5 or in a similar thermodynamic cycle if the cis chlorohydrin is an intermediate. The cis/trans tetrol product ratio will then be determined by the transition-state energy difference for an attack of water on the two carbocation conformations **2a** and **b** (Curtin−Hammett principle)[22] and will be independent of the nature of the halide ion or the cis/trans stereochemistry of chlorohydrin intermediates. The fact that the yields of cis tetrol from the acid-catalyzed hydrolysis of **1** in solutions of chloride, bromide, and iodide ions, extrapolated to infinite halide ion concentrations, are identical within experimental error[7] supports this conclusion and provides evidence that bromide and iodide ions also catalyze the interconversion of **2a** and **b**.

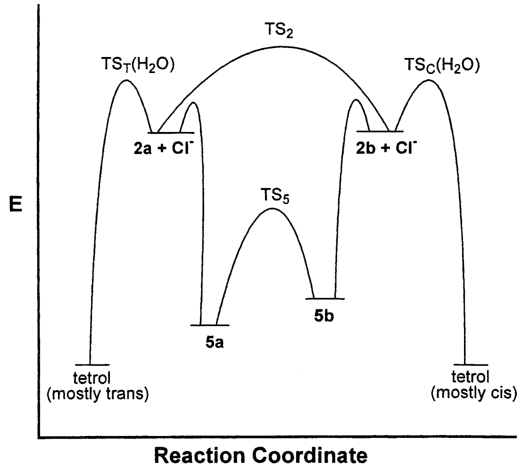


***Figure 2.*** Plots of free energy (*E*) vs Reaction Coordinate representing the direct and chloride ion-catalyzed interconversions of carbocations **2a** and **b** and the reactions of **2a** and **b** with water as outlined in Scheme 4 under conditions of high chloride ion concentrations. The reaction of diol epoxide **1** with $H^+$ to yield **2a** is not shown.

A free energy diagram that illustrates in a qualitative way the mechanism by which chloride ion catalyzes the interconversion of carbocation conformations **2a** and **b** by way of trans chlorohydrin **5** is given in Figure 2. In this diagram, the energy of the transition state for the interconversion of **2a** and **b** ($TS_2$) must be greater than the transition-state energies for reactions of **2a** and **b** with water, $TS_T(H_2O)$, and $TS_C(H_2O)$, respectively. In the presence of sufficient concentrations of chloride ion, however, the rate of reaction of **2a** with chloride ion to form **5a** by an axial attack of chloride on **2a** exceeds that of **2a** with water. It has been determined from a previous study that the minimum value of $k_{-1}/k_s$ in 10:90 dioxane−water is 12 $M^{-1}$,[7] and the common ion rate depression for reaction of **5** in 50:50 dioxane−water (Experimental Section) yields a value of 23 $M^{-1}$ for $k_{-1}/k_s$. From the analysis of the $^1H$ NMR coupling constants of **5** (Experimental Section), conformation **5a** is more stable than conformation **5b**. The free energy for the conformational inversion of **5a** to **5b** is expected to be equal to or greater than that for the conformational inversion of carbocation **2a** to carbocation **2b**. However, chlorohydrin **5** is much more stable than carbocation **2** plus chloride ion under these conditions,[23] and the lower energy pathway from **2a** to **2b** will be via

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(21) Calculated structures, energies, Cartesian coordinates of **5a** and **b** and a transition structure for the interconversion of **5a** and **b** are provided as Supporting Information.

(22) (a) Curtin, D. Y. *Rec. Chem. Prog.* **1954**, *15*, 111. (b) Eliel, E. L. *Stereochemistry of Carbon Compounds*; McGraw-Hill: New York, 1962; pp 151−152.

(23) With values of 23 $M^{-1}$ for $k_{-1}/k_s$ (Scheme 3, this study) and $2 \times 10^7$ $s^{-1}$ for $k_s$ (ref 5), the rate constant for the reaction of carbocation **2** with 1 M $Cl^-$ is $\sim 10^8$ $s^{-1}$. The rate constant for the ionization of **5** to form carbocation **2** in 1:1 dioxane−water is $\sim 0.2$ $s^{-1}$. The equilibrium between **5** and carbocation **2** under the conditions of this study, therefore, greatly favors the chlorohydrin.

chlorohydrin **5**. Thus, chloride ion catalyzes the interconversion of **2a** and **b**.

A second possible mechanism for the chloride ion-catalyzed interconversion of carbocation conformations **2a** and **b** involves a cis chlorohydrin intermediate. This intermediate could be formed by an “equatorial” attack of chloride ion on carbocation **2a**, an “axial” attack of chloride ion on **2b**, or by an $S_N2$ reaction of chloride ion with trans chlorohydrin **5**. Although the cis chlorohydrin may be sufficiently less stable than the trans chlorohydrin so that it cannot be detected in the reaction mixture, it cannot be ruled out as an intermediate in the conformational isomerization of **2a** to **2b**.

The hydrolysis of chlorohydrin **5** in 10:90 dioxane−water that does not contain external chloride ion yields trans and cis tetrols in a 79:21 ratio. This ratio is somewhat different than the ratio of trans and cis tetrols (65:35) formed from reaction of either **5** or **1** in solutions of high chloride ion concentrations. This observation is also consistent with the mechanism of Scheme 5. At high chloride ion concentrations, the cis:trans tetrol ratio depends on the transition-state energy difference for an attack of water on carbocation conformations **2a** and **b**. However, in the absence of chloride ion, the ratio of tetrols will depend on the transition-state energy difference for the formation of carbocation conformations **2a** and **b**. This will be true because carbocation formation is rate-limiting for the reaction of **5** in the absence of added chloride ion, and each carbocation conformation reacts with water faster than it isomerizes to the other conformation. The fact that a significant yield of cis tetrol (20%) is formed from the hydrolysis of trans chlorohydrin **5** in the absence of added external chloride ion, where carbocation formation is rate-limiting and cis chlorohydrin is unlikely to form by any of the mechanisms listed above, suggests that the major pathway leading to carbocation conformation **2b** is via the trans chlorohydrin.

If carbocation conformation **2b** undergoes energetically favorable axial attack by water to yield cis tetrol as the major product, then an axial attack of other similar nucleophiles on **2b** leading to cis products should also be observed. The observations that chlorohydrin **5** reacts with deoxyadenosine and DNA to yield mostly cis adducts[8] might, therefore, be due to a mechanism involving an axial attack of the nucleic acid base on conformation **2b**. Studies to determine the stereochemistry of the reactions of nucleophiles other than water on carbocation conformations **2a** and **b** are in progress.

## Summary

We propose that the carbocation intermediate formed from the acid-catalyzed hydrolysis of diol epoxide **1** and from the hydrolysis of chlorohydrin **5** exists in two conformations, with an energy barrier to interconversion that is greater than the energy barriers for their reactions with water. This is an example where rate and product studies clearly demonstrate that two discrete carbocation conformations are not at conformational equilibrium in water solution. However, the interconversion of these two carbocation conformations is catalyzed by chloride ion, and in water solutions with high chloride ion concentrations, the two conformations do interconvert rapidly relative to the rates at which they react with water. The ratio of cis 9,10- and trans 9,10-tetrols formed from both the reactions of **1** and **5** depends only on the transition-state energy difference for the attack of water on the two carbocation conformations when the concentration of chloride ion is sufficiently high, so that the two carbocation conformations are at equilibrium. However, the ratio of cis and trans tetrols formed from the hydrolysis of chlorohydrin **5** in the absence of external chloride ion depends on the transition-state energy difference for the formation of the two carbocation conformations.

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**Supporting Information Available:** Figure with plot of log $k_{obsd}$ versus pH for the reaction of 7$\beta$,8α,9α-trihydroxy-10$\beta$-chloro-7,8,9,10-tetrahydrobenzo[*a*]pyrene (chlorohydrin **5**) in 1:1 dioxane−water, 0.2 M NaCl; $H^1$ NMR spectrum of chlorohydrin **5**; calculated structures and Cartesian coordinates of carbocation conformations **2a** and **b** (ab initio B3LYP/6-31G*); calculated transition structure for the interconversion of **2a** and **b** (ab initio B3LYP/6-31G*); calculated structures and Cartesian coordinates of chlorohydrin conformations **5a** and **b** (ab initio HF/6-31G*); calculated transition structure for the interconversion of **5a** and **b** (ab initio HF/6-31G*). This material is available free of charge via the Internet at http://pubs.acs.org.

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